

LEVOCARNITINE - levocarnitine solution
Rising Pharmaceuticals, Inc.

Levocarnitine Oral Solution USP

1g/10mL

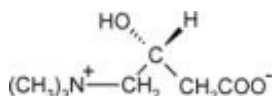
(118mL multidose)

For oral use only. **Not for parenteral use.**

DESCRIPTION

Levocarnitine is a carrier molecule in the transport of long-chain fatty acids across the inner mitochondrial membrane.

The chemical name of levocarnitine is 3-carboxy-2(R)-hydroxy-N,N,N-trimethyl-1-propanaminium, inner salt. Levocarnitine is a white crystalline, hygroscopic powder. It is readily soluble in water, hot alcohol, and insoluble in acetone. The specific rotation of levocarnitine is between -29° and -32°. Its chemical structure is:



Molecular Formula: C₇H₁₅NO₃

Molecular Weight: 161.20

Levocarnitine Oral Solution USP is intended solely for oral administration. Each 10 mL contains 1 gram of levocarnitine. Levocarnitine Oral Solution USP is available as 1 g/10 mL in bottles of 118 mL with the following inactive ingredients: Artificial Cherry Flavor, D,L,-Malic Acid, Purified Water, Sucrose Syrup. Methylparaben NF and Propylparaben NF are added as preservatives. The pH is approximately 5.

CLINICAL PHARMACOLOGY

Levocarnitine is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, thereby delivering substrate for oxidation and subsequent energy production. Fatty acids are utilized as an energy substrate in all tissues except the brain. In skeletal and cardiac muscle, fatty acids are the main substrate for energy production.

Primary systemic carnitine deficiency is characterized by low concentrations of levocarnitine in plasma, RBC, and/or tissues. It has not been possible to determine which symptoms are due to carnitine deficiency and which are due to an underlying organic acidemia, as symptoms of both abnormalities may be expected to improve with Levocarnitine Oral Solution USP. The literature reports that carnitine can promote the excretion of excess organic or fatty acids in patients with defects in fatty acid metabolism and/or specific organic acidopathies that bioaccumulate acylCoA esters.¹⁻⁶

Secondary carnitine deficiency can be a consequence of inborn errors of metabolism. Levocarnitine Oral Solution USP may alleviate the metabolic abnormalities of patients with inborn errors that result in accumulation of toxic organic acids. Conditions for which this effect has been demonstrated are: glutaric aciduria II, methyl malonic aciduria, propionic acidemia, and medium chain fatty acylCoA dehydrogenase deficiency.^{7,8} Autointoxication occurs in these patients due to the accumulation of acylCoA compounds that disrupt intermediary metabolism. The subsequent hydrolysis of the acylCoA compound to its free acid results in acidosis which can be life-threatening. Levocarnitine clears the acylCoA compound by formation of acylcarnitine, which is quickly excreted. Carnitine deficiency is

defined biochemically as abnormally low plasma concentrations of free carnitine, less than 20 µmol/L at one week post term and may be associated with low tissue and/or urine concentrations. Further, this condition may be associated with a plasma concentration ratio of acylcarnitine/levocarnitine greater than 0.4 or abnormally elevated concentrations of acylcarnitine in the urine. In premature infants and newborns, secondary deficiency is defined as plasma levocarnitine concentrations below age-related normal concentrations.

PHARMACOKINETICS

In a relative bioavailability study in 15 healthy adult male volunteers, levocarnitine tablets were found to be bio-equivalent to levocarnitine oral solution. Following 4 days of dosing with 6 tablets of levocarnitine 330 mg b.i.d. or 2 g of levocarnitine oral solution b.i.d., the maximum plasma concentration (C_{max}) was about 80 µmol/L and the time to maximum plasma concentration (T_{max}) occurred at 3.3 hours.

The plasma concentration profiles of levocarnitine after a slow 3 minute intravenous bolus dose of 20 mg/kg of levocarnitine were described by a two-compartment model. Following a single i.v. administration, approximately 76% of the levocarnitine dose was excreted in the urine during the 0-24h interval. Using plasma concentrations uncorrected for endogenous levocarnitine, the mean distribution half life was 0.585 hours and the mean apparent terminal elimination half life was 17.4 hours.

The absolute bioavailability of levocarnitine from the two oral formulations of levocarnitine, calculated after correction for circulating endogenous plasma concentrations of levocarnitine, was 15.1 ± 5.3% for levocarnitine tablets and 15.9 ± 4.9% for levocarnitine oral solution USP.

Total body clearance of levocarnitine (Dose/AUC including endogenous baseline concentrations) was a mean of 4.00 L/h.

Levocarnitine was not bound to plasma protein or albumin when tested at any concentration or with any species including the human.⁹

METABOLISM AND EXCRETION

In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [³H-methyl]-L-carnitine following 15 days of a high carnitine diet and additional carnitine supplement, 58 to 65% of the administered radioactive dose was recovered in the urine and feces in 5 to 11 days. Maximum concentration of [³H-methyl]-L-carnitine in serum occurred from 2.0 to 4.5 hr after drug administration. Major metabolites found were trimethylamine N-oxide, primarily in urine (8% to 49% of the administered dose) and [³H]-γ-butyrobetaine, primarily in feces (0.44% to 45% of the administered dose). Urinary excretion of levocarnitine was about 4 to 8% of the dose. Fecal excretion of total carnitine was less than 1% of the administered dose.¹⁰

After attainment of steady state following 4 days of oral administration of Levocarnitine Oral Solution USP (2000 mg q12h) to 15 healthy male volunteers, the mean urinary excretion of levocarnitine during a single dosing interval (12h) was about 9% of the orally administered dose (uncorrected for endogenous urinary excretion).

INDICATIONS AND USAGE

Levocarnitine Oral Solution USP is indicated in the treatment of primary systemic carnitine deficiency. In the reported cases, the clinical presentation consisted of recurrent episodes of Reye-like encephalopathy, hypoketotic hypoglycemia, and/or cardiomyopathy. Associated symptoms included hypotonia, muscle weakness and failure to thrive. A diagnosis of primary carnitine deficiency requires that serum, red cell and/or tissue carnitine levels be low and that the patient does not have a primary defect in fatty acid or organic acid oxidation (see Clinical Pharmacology). In some patients, particularly those presenting with cardiomyopathy, carnitine supplementation rapidly alleviated signs and symptoms. Treatment should include, in addition to carnitine, supportive and other therapy as indicated by the

condition of the patient.

Levocarnitine Oral Solution USP is also indicated for acute and chronic treatment of patients with an inborn error of metabolism which results in a secondary carnitine deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

None.

PRECAUTIONS

General

Levocarnitine Oral Solution USP is for oral/internal use only.

Not for parenteral use.

Gastrointestinal reactions may result from a too rapid consumption of carnitine. Levocarnitine Oral Solution USP may be consumed alone, or dissolved in drinks or other liquid foods to reduce taste fatigue. It should be consumed slowly and doses should be spaced evenly throughout the day to maximize tolerance.

The safety and efficacy of oral levocarnitine has not been evaluated in patients with renal insufficiency. Chronic administration of high doses of oral levocarnitine in patients with severely compromised renal function or in ESRD patients on dialysis may result in accumulation of the potentially toxic metabolites, trimethylamine (TMA) and trimethylamine-N-oxide (TMAO), since these metabolites are normally excreted in the urine.

Carcinogenesis, mutagenesis, impairment of fertility

Mutagenicity tests performed in *Salmonella typhimurium*, *Saccharomyces cerevisiae*, and *Schizosaccharomyces pombe* indicate that levocarnitine is not mutagenic. No long-term animal studies have been performed to evaluate the carcinogenic potential of levocarnitine.

Pregnancy

Pregnancy Category B.

Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose on the basis of surface area and have revealed no evidence of impaired fertility or harm to the fetus due to Levocarnitine Oral Solution USP. There are, however, no adequate and well controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Levocarnitine supplementation in nursing mothers has not been specifically studied.

Studies in dairy cows indicate that the concentration of levocarnitine in milk is increased following exogenous administration of levocarnitine. In nursing mothers receiving levocarnitine, any risks to the child of excess carnitine intake need to be weighed against the benefits of levocarnitine supplementation to the mother. Consideration may be given to discontinuation of nursing or of levocarnitine treatment.

Pediatric Use

See Dosage and Administration.

ADVERSE REACTIONS

Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or D,L-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild myasthenia has been described only in uremic patients receiving D,L-carnitine. Gastrointestinal adverse reactions with Levocarnitine Oral Solution USP dissolved in liquids might be avoided by a slow consumption of the solution or by a greater dilution. Decreasing the dosage often diminishes or eliminates drug-related patient body odor or gastrointestinal symptoms when present. Tolerance should be monitored very closely during the first week of administration, and after any dosage increases.

Seizures have been reported to occur in patients with or without pre-existing seizure activity receiving either oral or intravenous levocarnitine. In patients with pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported.

To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharmaceuticals, Inc. at 1-866-562-4597 or FDA at 1-800-FDA-1088 or www.FDA.gov/medwatch.

OVERDOSAGE

There have been no reports of toxicity from levocarnitine overdose. Levocarnitine is easily removed from plasma by dialysis. The intravenous LD₅₀ of levocarnitine in rats is 5.4 g/kg and the oral LD₅₀ of levocarnitine in mice is 19.2 g/kg. Large doses of levocarnitine may cause diarrhea.

DOSAGE AND ADMINISTRATION

Levocarnitine Oral Solution USP.

For oral use only. **Not for parenteral use.**

Adults: The recommended dosage of levocarnitine is 1 to 3 g/day for a 50 kg subject, which is equivalent to 10 to 30 mL/day of Levocarnitine Oral Solution USP. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 1 g/day, (10 mL/day), and be increased slowly while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

Infants and children: The recommended dosage of levocarnitine is 50 to 100 mg/kg/day which is equivalent to 0.5 mL/kg/day Levocarnitine Oral Solution USP. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 50 mg/kg/day, and be increased slowly to a maximum of 3 g/day (30 mL/day) while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

Levocarnitine Oral Solution USP may be consumed alone or dissolved in drink or other liquid food. Doses should be spaced evenly throughout the day (every three or four hours) preferably during or following meals and should be consumed slowly in order to maximize tolerance.

HOW SUPPLIED

Levocarnitine Oral Solution USP is supplied in 118 mL (4 FL. OZ.) multiple-dose plastic containers. The multiple-dose containers are packaged 24 per case (NDC 64980-503-12). Store at 20° to 25°C (68° to 77°F); excursion permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Rx only.

REFERENCES

1. Bohmer, T., Rydning, A. and Solberg, H.E. 1974. Carnitine levels in human serum in health and disease. *Clin. Chim. Acta* 57:55-61.
2. Brooks, H., Goldberg, L., Holland, R. et al. 1977. Carnitine-induced effects on cardiac and peripheral hemodynamics. *J. Clin. Pharmacol.* 17:561-568.
3. Christiansen, R., Bremer, J. 1976. Active transport of butyrobetaine and carnitine into isolated liver cells. *Biochim. Biophys. Acta* 448:562-577.
4. Lindstedt, S. and Lindstedt, G. 1961. Distribution and excretion of carnitine in the rat. *Acta Chem. Scand.* 15:701-702.
5. Rebouche, C.J. and Engel, A.G. 1983. Carnitine metabolism and deficiency syndromes. *Mayo Clin. Proc.* 58:533-540.
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7. Scriver, C.R., Beaudet, A.L., Sly, W.S. and Valle, D. 1989. *The Metabolic Basis of Inherited Disease*. New York: McGraw-Hill.
8. Schaub, J., Van Hoof, F. and Vis, H.L. 1991. *Inborn Errors of Metabolism*. New York: Raven Press.
9. Marzo, A., Arrigoni Martelli, E., Mancinelli, A., Cardace, G., Corbellella, C., Bassani, E. and Solbiati, M. 1991. Protein binding of L-carnitine family components. *Eur. J. Drug Met. Pharmacokin.*, Special Issue III: 364-368.
10. Rebouche, C.J. 1991. Quantitative estimation of absorption and degradation of a carnitine supplement by human adults. *Metabolism* 40:1305-1310.

Distributed by:

Rising Pharmaceuticals, Inc.
Saddle Brook, NJ 07663

Manufactured by:

Lyne Laboratories, Inc.
Brockton, MA 02301

R6-12/17

Active ingredient: L-carnitine 1 g/10mL

Usual Dosage: See package insert.

Avoid excess heat. Protect from freezing. Store at 20°- 25°C (68°-77°F) excursion permitted to 15°-30°C (59°- 86°F). [See USP Controlled Room Temperature].

Distributed by:

Rising Pharmaceuticals, Inc.
Saddle Brook, NJ 07663

Manufactured by:

Lyne Laboratories, Inc.
Brockton, MA 02301

R6-12/17

PRINCIPAL DISPLAY PANEL

NDC 64980-503-12

Rising®

Levocarnitine

Oral Solution USP

L-carnitine 1 g/10 mL

118 mL (4 fl. oz.)

Multiple Dose Container

Rx only

NDC 64980-503-12

Rising®

**Levocarnitine
Oral Solution USP**

L-carnitine 1 g/10 mL

118 mL (4 fl. oz.)
Multiple Dose Container

Rx only

Active ingredient: L-carnitine 1 g/10mL

Inactive Ingredients: Artificial Cherry Flavor, D, L-Malic Acid, Methylparaben NF, Propylparaben NF, Purified Water, Sucrose Syrup

Usual Dosage: See package insert.

Avoid excess heat. Protect from freezing. Store at 20°-25°C (68°-77°F) excursion permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

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R6-12/17

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LEVOCARNITINE

levocarnitine solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:64980-503
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
LEVO CARNITINE (UNII: 0G389FZZ9M) (LEVOCARNITINE - UNII:0G389FZZ9M)	LEVOCARNITINE	1 g in 10 mL

Inactive Ingredients

Ingredient Name	Strength
MALIC ACID (UNII: 817L1N4CKP)	
WATER (UNII: 059QF0KO0R)	
SUCROSE (UNII: C151H8M554)	
METHYL PARABEN (UNII: A2I8C7HI9T)	
PROPYL PARABEN (UNII: Z8IX2SC1OH)	

Product Characteristics

Color		Score	
Shape		Size	
Flavor	CHERRY (CHERRY)	Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64980-503-12	118 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	09/20/2004	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076851	09/20/2004	

Labeler - Rising Pharmaceuticals, Inc. (041241766)**Registrant** - Lyne Laboratories, Inc. (053510459)**Establishment**

Name	Address	ID/FEI	Business Operations
Lyne Laboratories, Inc.		053510459	MANUFACTURE(64980-503)

Revised: 10/2018

Rising Pharmaceuticals, Inc.